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Title: Observational Study of Neural Respiratory Drive during Sleep at High Altitude

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Running title: Neural Respiratory Drive at Altitude

Abstract

Aims: Ventilation at altitude changes due to altered levels of pO_2 , pCO_2 and the effect on blood pH. Nocturnal ventilation is particularly exposed to these changes. We hypothesized that increasing neural respiratory drive is associated with the severity of sleep-disordered breathing at altitude.

Methods: Mountaineers were studied at sea level (London, UK), and at altitude at the Aconcagua (Andes, Argentina). Neural respiratory drive (NRD) was measured as electromyogram of the diaphragm (EMGdi) overnight by a transoesophageal multi-electrode catheter and results reported for sea level, 3,380m, 4,370m and 5,570m.

Results: Four healthy subjects (3 male, age 31(3)years, body-mass-index 23.6(0.9)kg/m², neck circumference 37.0(2.7)cm, FEV₁ 111.8(5.1)%predicted, FVC 115.5(6.3)%predicted) were studied. No subject had significant sleep abnormalities at sea level. Time to ascent to 3,380m was one day, to 4,370m five days, and the total nights at altitude was 21 days. The oxygen desaturation index (4%ODI 0.8(0.4), 22.0 (7.2), 61.4 (26.9), 144.9/hour, respectively) and the EMGdi (5.2 (1.9), 12.8 (5.1), 14.1 (3.4), 18.5%, respectively) increased with the development of periodic breathing at altitude, while the average SpO₂ declined (97.5 (1.3), 84.8 (0.5), 81.0 (4.1), 68.5%, respectively). The average EMGdi correlated well with the 4%ODI ($r=0.968$, $p=0.032$).

Conclusion: Neural respiratory drive during sleep increases at altitude in relation to the severity of periodic breathing.

Key Words: Sleep, periodic breathing, sleep apnoea, diaphragm, electromyography

Introduction

Respiratory control at altitude differs from that at sea level in the awake (Khoo et al. 1982) and asleep normal subjects (Bloch et al. 2010). While awake, it enables people at altitude to vary their respiratory pattern and maintain oxygen saturation (Hermand et al. 2015). At sea level breathing becomes more shallow with sleep onset and, at altitude, this decrease in ventilation leads to increased levels of hypoxia (Colrain et al. 1987). In response to the developing hypoxia a compensatory hyperventilation results in hypocapnia and respiratory alkalosis, and with low levels of carbon dioxide ($p\text{CO}_2$) the apnoea threshold is reached (Xie et al. 2001). As a consequence of the time delay in response to the apnoea the carbon dioxide levels rise and the oxygen levels drop, which explains the periodic occurrence of hyperventilation and apnoeas, described as Cheyne-Stokes-Ventilation (Harrison et al. 1934).

Neural respiratory drive (NRD), as measured by the electromyography of the diaphragm (EMGdi), is closely correlated with breathlessness (Reilly et al. 2011, Jolley et al. 2015, Jolley and Moxham 2016) and can be recorded breath-by-breath while patients are asleep (Steier et al. 2010, Xiao et al. 2014).

We hypothesized that sleep-disordered breathing at altitude is closely correlated with NRD, and that high levels of NRD would lead to increasing numbers of apnoeas and a greater severity of sleep disordered breathing with ascent to high altitude.

Participants and Methods

This study was planned as part of a programme to assess “Neural Respiratory Drive in cardiopulmonary conditions and normal subjects”, it was approved by the local research ethics’ committee at King’s College London, UK (Reference number: 05/Q0703/82; V3-21/02/2006). Informed written consent was obtained prior to inclusion by all participants.

An expedition to the Aconcagua, Argentina (peak altitude 6,962m) was planned to assess NRD in asleep healthy volunteers. For this purpose four mountaineers were recruited and initially studied in the sleep laboratory at sea level (King’s College Hospital, London, UK). Exclusion criteria were any medical conditions that could put participation during a mountaineering expedition at altitude at risk; only young healthy subjects were recruited. We recorded demographics, spirometry, full polysomnography, tests of respiratory muscle strength and baseline recordings of the EMG of the diaphragm and the parasternal intercostal muscles. The equipment was taken for a test to the International Foundation High Altitude Research Station Jungfrauoch, CH (November 2007; altitude 3,450m). The expedition to the Aconcagua started in December 2007 and finished at the end of January 2008 ascending via Confluencia (3,380m), Plaza de Mulas (4,370m), Camp Canada (5,050m), Camp Alaska (5,200m), and Nido de Condore (5,570m), but overnight sleep studies were performed at 3,380m, 4,370m and 5,570m only. For reasons of safety, a stop of at least two days at each level of altitude was planned. All mountaineers passed a medical examination prior to commencing the climb and again at Plaza de Mulas (4,370m), none showed any of the following signs or symptoms of altitude sickness or pulmonary oedema:

Symptoms:

- Difficulty in breathing at rest
- Cough
- Weakness or decreased exercise performance
- Chest tightness or congestion

Signs:

- Crackles or wheezing in at least one lung field
- Central cyanosis
- Tachypnoea
- Tachycardia

The recording equipment stopped working after the 1st night at Nido de Condores (5,570m), only one sleep study (subject JS) could be obtained.

Demographics

At baseline, age (years), gender (male/female), height (m) and weight (kg) were recorded, and body mass index (BMI) was calculated (kg/m^2). To assess the risk of sleep-disordered breathing, neck circumference (cm) was measured using a standard tape measure.

Spirometry

Baseline spirometry was recorded following calibration of the equipment using a 3L syringe (Vitalograph®, Buckingham, England), seated with a noseclip on and using a tube mouthpiece. The recording spirometer was a Vitalograph Gold Standard

(Vitalograph[®], Buckingham, England). The participants were asked to breathe in slowly to total lung capacity (TLC) and then to blow out as fast and hard as they could to measure the forced expiratory volume in one second (FEV₁) and the forced vital capacity (FVC). The manoeuvres were repeated at least five times, until consistent results were obtained according to ATS/ERS criteria for the standardization of spirometry {Miller, 2005 #833}.

Respiratory muscle tests

Tests of inspiratory and expiratory muscle strength were performed following baseline spirometry. The participants were seated and for the mouth pressure measurements a flanged mouthpiece was used, with a noseclip on; for the sniff pressure measurement a sniff plug was inserted into one nostril (Heritier et al. 1994). The maximum inspiratory mouth and the sniff nasal pressures were recorded from functional residual capacity (FRC) while the maximum expiratory mouth pressure was recorded from TLC. A handheld portable pressure meter (MicroRPM[®] Respiratory Muscle Testing, Carefusion[®], Basingstoke, UK) was used to record the pressures.

Polysomnography

A full polysomnography was performed using Alice5[®] equipment (Respironics[®], Murrysville, PA, USA) at sea level. Electrical activity of the brain (EEG) was measured with surface electrodes (Gold), according to the ten-twenty system we recorded F4/M1, C4/M1 and O2/M1. Sleep and respiratory events were scored with standard terminology (Iber et al. 2007). Electro-oculography (EOG) was measured by Gold surface electrodes to detect rapid eye movements (REM). A

position electrode measured on which side the patient was lying. Pulse oximetry sensed the oxygen saturation and heart rate. Airflow was detected via a nasal cannula (sensing pressure) and an oronasal thermistor. Abdominal and chest wall movements were detected via uncalibrated inductance plethysmography bands around the chest and abdomen. Apnoeas were defined as no airflow for >10s, hypopnoeas were defined as periods of reduced airflow <50% from baseline for >10s. Obstructive episodes were scored if there was ongoing inspiratory effort measured during apnoeas or hypopnoeas; the events were scored as central if ventilatory effort was absent. Respiratory effort related arousals were scored if an arousal occurred following a period of >10s with increased inspiratory effort which did not meet the criteria of apnoea or hypopnoea.

Pulse oximetry

During ascent to altitude, pulse oximetry (Nonin Medical Inc[®], Plymouth, MN/USA) recorded an average of 30.5 (4.3) hours for the subjects. Each mountaineer had an overnight pulse oximetry combined with EMG recordings at 3,380m and at 4,370m, recording was only possible in one mountaineer at 5,570m. The data were analysed upon return to London and average oxygenation (SpO₂), nadir and the 4% oxygen desaturation index (ODI) were calculated.

Electromyography

A multipair electrode catheter (Yinghui Medical Tech Ltd[®], Guangzhou, China) was inserted via one nostril to record the transoesophageal EMGdi, as previously described (Luo et al. 2008, Steier et al. 2010), connected to RA-8[®] amplifiers (Yinghui Medical Tech Ltd[®], Guangzhou, China) that further transmitted the signal to

an analog-to-digital converter, Powerlab[®] 16/30 running Chart[®] Version 5 (ADInstruments[®], Colorado Springs/CO, USA).

The EMG of the neck muscles, parasternal intercostals, and abdominal muscles was recorded using surface electrodes (Kendall Arbo[®], Tyco Healthcare[®], Neustadt, Germany) from standard positions (White et al. 1995, Maarsingh et al. 2000, Konrad et al. 2001, Duivermann et al. 2004, Lasserson et al. 2006). The surface electrodes were positioned on the sternocleidomastoid (neck) muscle bilaterally 2cm above the clavicle and 3cm beneath the mastoid process (EMGneck). A reference electrode was placed on the skin 6cm lateral to the midline below the clavicles. For recording the EMG of the parasternal intercostals (EMGpara) electrodes were placed on each side of the sternum 3cm from the midline in the second intercostal space (Reilly et al. 2011). The EMG of the abdominal muscles (EMGabdomen) was recorded from electrodes 2-3cm lateral to the umbilicus bilaterally over the region of the rectus abdominis.

The EMG was recorded during resting breathing and during the manoeuvres that have been described to achieve maximum or close to maximum activation of the diaphragm; whilst breathing in to total lung capacity (TLC manoeuvre), whilst breathing in as hard as possible against a closed airway (PI_{max} manoeuvre), maximal sniffs, and maximum voluntary ventilation for 15s (“sprint MVV”). Additionally, EMG was recorded during maximal expiration against an occluded valve (PE_{max} manoeuvre). Manoeuvres were repeated until consistent results were achieved, at least five times, and the maximum of all manoeuvres was then selected to represent 100% activity. The recordings of the spontaneous EMG were sampled at 1kHz, and EMG

data were filtered with a high-pass 30 Hz and an additional low pass 1kHz filter. The rectified signals of the EMG (root-mean-square of the raw data) were quantified and transformed into percent of maximum activity (as derived from the maximum inspiratory and expiratory manoeuvres described above).

The equipment was powered by two Victron Energy AMG GEL 12-35 batteries (120 Ah; Victron Energy, Nuneaton, UK) that were connected to a Phoenix Inverter 12/350 / Blue Power Charger 45-65Hz, 200W 12V/15A (Victron Energy, Nuneaton, UK), and charged by six standard flexible outdoor solar panels (560 x 1490 mm, 12V/140W).

All EMG channels (diaphragm, neck, parasternal, abdomen) were recorded at sea level. At altitude, the EMG of the diaphragm (transoesophageal), the parasternal intercostals and the abdominal muscles (surface EMG) were recorded and analysed. The placement of the transoesophageal multipair electrode catheter allows the recording of five channels around the electrically active region of diaphragm. The positioning of the oesophagel catheter is such that channel 1 and channel 5 provide the largest recorded signal which are then selected for analysis (root mean square, time constant 100ms of the peak signal), as previously described.⁸⁻¹⁰ The ‘absolute level of NRD’ is defined as the recorded percentage of maximum activity allowing the comparison of levels of drive between different subjects and different conditions, as described by our group^{6,9,11-13} and others.¹⁴ To obtain an average of the NRD, each non-periodic breath during a one-minute period at the end of each ten-minute period at night was analysed and included, if variability of the signal was less than 25% from baseline. These one-minute data blocks were summed and the mean of the sum of

these values taken for the whole night to calculate the average level of NRD (baseline).

The occurrence of cyclical changes in a biosignal, e.g. during periodic breathing but also commonly observed during obstructive sleep apnoea, makes analysis difficult. It requires the description of an average baseline and of the deviation from that baseline. In respiratory sleep medicine this is achieved by reporting the average nocturnal SpO₂ plus the number of desaturation events (oxygen desaturation index, ODI). In the analysis of the EMG signals, a similar approach was achieved by providing the average EMG between apnoeas to provide the baseline plus the slopes of the EMG signal (decrecendo, crescendo) prior to and following central apnoeic events, as previously described in other forms of sleep-disordered breathing,^{9,12,13} as well as the index of respiratory events.

Outcome parameters

In order to define the correlation between NRD and sleep-disordered breathing the level of neural respiratory drive, as measured by the EMGdi (%max), was recorded at each level of altitude and differential respiratory muscle recruitment, as expressed by the EMG activity of different muscle groups, was further correlated to abnormal breathing patterns. Other outcomes were the apnoea threshold of NRD and the EMGdi that was associated with central sleep apnoeas, as well as the oxygen desaturation index (4%ODI), the mean and nadir nocturnal SpO₂, and the surface EMG of the parasternal intercostal and abdominal muscles. Sleep studies with recording of the EMG and nocturnal pulse oximetries were performed the first night when ascending to a new altitude. Time to ascent to 3,380m was one day, to 4,370m five days, and to 5,570m thirteen days; the total of nights spent at altitude was 21

days.

Statistical analysis

SPSS® Version 20.0 (SPSS® Inc, Chicago, IL/USA) was used for the analysis. Results are reported as mean (standard deviation, SD) for all normally distributed test results, results represent the average data of the first night at a new altitude. The small sample size of the group with multiple comparisons at different altitudes precluded the use of many statistical tests and, instead, we decided to report the 95% Confidence Interval (95%CI) to provide information about overlap of the group's means. Significance was accepted with a p-value <0.05.

Results

Four healthy mountaineers were studied at sea level and during ascent to altitude. The group was young, predominantly male, normal in weight and without any obvious respiratory abnormalities (Table 1).

The global inspiratory, diaphragm and expiratory muscle strength was normal. Respiratory muscle EMG recordings revealed diaphragm and parasternal activity while awake similar to that observed in normal subjects (Steier et al. 2010), as well as low neck muscle and expiratory muscle activity (Table 2).

The polysomnography at sea level, revealed a short sleep time with preserved sleep architecture and a relatively normal sleep efficiency. There were no respiratory abnormalities, no significant apneas or hypopnoeas were observed, and there was no hypoventilation (Table 3).

Sleep-disordered breathing developed with increasing altitude in all subjects and the severity increased with higher altitude, leaving all subjects with severe central sleep apnoea and periodic breathing (Table 4). Recordings at 5,570m were obtained only in one subject who had a 4%ODI of $144.9 \times h^{-1}$, mean SpO₂ of 68.5% and a nadir SpO₂ of 50.4%.

The EMG recordings at different altitudes showed increased variability that was associated with the development of sleep-disordered breathing. Cyclical crescendo-decrescendo patterns of inspiratory EMG activity were observed during most of the night (Figure 1).

Following sleep onset, EMG activity decreased significantly at sea level. At 3,380m increased EMG activity of the diaphragm, the parasternal intercostals and the abdominal muscles was observed throughout the night. This activity did not increase significantly with further ascent to an altitude of 4,370m (Table 4).

There was a positive correlation between the 4%ODI at 4,370m and the EMGdi at 3,380m ($r=0.97$, $p=0.03$) as well as a negative correlation with the EMGparasternal at sea level ($r=-0.96$, $p=0.04$) and at 4,370m ($r=-0.97$, $p=0.03$). There was also an inverse relationship between the EMGdi at 3,380m and the EMGparasternal at 4,370m ($r=-0.99$, $p<0.01$).

The cyclical occurrence of highly variable inspiratory activity when breathing asleep at altitude made it difficult to analyse stable periods of EMG activity and calculate averages (Figure 2).

Discussion

Neural respiratory drive, as measured by the diaphragm EMG, increases with high altitude as a response to hypobaric environmental conditions. The increased levels of drive are directly associated with the development of sleep disordered breathing. The apnoea threshold during periodic breathing is reached when EMGdi activity falls to levels below 5% maximum, the level required for resting breathing at sea level, and breathing resumes again when approximately 10% of maximum EMGdi activity is reached following central apnoea. To support diaphragm activity, extra-diaphragmatic muscles are recruited when asleep at altitude to achieve sufficient ventilation.

Clinical significance

In response to hypobaric conditions, a high neural respiratory drive at altitude increases ventilation to maintain oxygenation; this leads to intermittent hypocapnia with a respiratory alkalosis resulting in a Cheyne-Stokes respiration, particularly when asleep. The central apnoea threshold while asleep is reached when neural respiratory drive declines to a level lower than that required for resting breathing at sea level.

It has been established that human beings develop sleep-disordered breathing at altitude, but the accurate measurement of physiological parameters has been challenging. This is the first study at high altitude that has recorded the

transoesophageal crural diaphragm EMG from the electrical active region which allows the accurate measurement of central motor neuron output (Neural Respiratory Drive) in humans (Luo, Tang et al. 2009, Jolley and Moxham 2016). Knowledge about how subjects recruit respiratory muscle activity during sleep helps to understand the factors that determine acclimatisation to high altitude. The levels of EMGdi activity at altitude, expressed as percent of maximum, are similar to that in patients with moderate COPD, asthma, obesity hypoventilation syndrome and obstructive sleep apnoea (Luo et al. 2008, Jolley et al. 2009, Steier et al. 2009, Steier et al. 2010, Steier et al. 2011). Thus respiratory reserve is reduced with increasing altitude and, despite increased muscle recruitment, both hypoxaemia when awake and sleep disordered breathing deteriorate with ascent to altitude. Interestingly, a level of neural respiratory drive similar to that at sea level predicts the imminent onset of central apnoea, the so called apnoea threshold (Xie et al. 2001, Steier et al. 2010). During this five-week long expedition, the limited acclimatisation at each level of altitude did not significantly affect the apnoea threshold.

A high neural respiratory drive at altitude leads to a higher minute ventilation which results in more significant hypocapnia; this triggers apnoeas and oxygen desaturations, as indicated by the positive correlation between the EMG of the diaphragm and the oxygen desaturation index. However, in subjects who adopted a different breathing pattern at altitude by recruiting more chest wall muscle activity the sleep disordered breathing seemed to be less severe, as indicated by a negative correlation between the parasternal EMG and the ODI. In addition, central efferent output can be divided between different muscle groups at the same time. In the studied cohort at altitude, we recorded from the diaphragm and the parasternal EMG

to identify inspiratory muscle activity. The negative correlation between parasternal and diaphragm EMG indicates that the subject's respiratory pattern varied and, as parasternal activity was recruited, diaphragm EMG was diminished. Considering that the volume effect of parasternal intercostal muscle activity will be significantly lower than the contribution from increased diaphragm activity, it is likely that subjects with increased chest wall muscle activity will have experienced less significant hypocapnic episodes, resulting in less severe sleep disordered breathing.

These observations reflect the chemosensitivity to low levels of $p\text{CO}_2$ following a period of relative hyperventilation that is employed to control for hypoxaemia in hypobaric environmental conditions. During a central apnoeic event the $p\text{CO}_2$ level rises slowly back to normal levels which normalizes the pH, and the $p\text{O}_2$ then starts to fall again with a circulatory delay.

Limitations

This was an exploratory study in a small group of mountaineers, limited by the number of participants and the difficult logistics', allowing for hypothesis generation. However, data presentation using the 95% confidence interval and the reliable occurrence and analysis of periodic breathing at altitude with repeated measurements at different levels of altitude allow a "proof of concept" to validate the observations. The study was further limited by a lack of access to polysomnography equipment at altitude but, as the baseline study at sea level confirmed the absence of any sleep disordered breathing, the reporting of the oxygen desaturation index in parallel to the recording of electromyography provided valuable information to assess ventilation. The data recorded were from the first night at each level of altitude, therefore were

only available for a single night in each subject at each level. Future studies could be designed to understand the effect of acclimatization by recording subsequent nights in the same subjects.

Conclusion

Increased neural respiratory drive was associated with more severe sleep disordered breathing. Future research should investigate in detail whether there is a protective level of NRD and a gender effect predicting the ventilatory response at altitude.

Conflict of interest: The authors have no conflict of interest related to the content of this manuscript.

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Table legends:

Table 1: Demographics of participants (n=4). *BMI*, body mass, index; *FEV₁*, forced expiratory volume in 1s; *FVC*, forced vital capacity. Except for the gender ratio data are presented as mean (standard deviation; 95%CI).

Table 2: Respiratory muscle strength and activity while awake at sea level. *PI_{max}*, maximum inspiratory mouthpressure; *PE_{max}*, maximum expiratory mouthpressure; *Psniff, nasal*, maximum inspiratory sniff nasal pressure; EMG, electromyography. Data are presented as mean (standard deviation; 95%CI).

Table 3: Results of the polysomnography at sea level (London, UK; 0m). *TST*, total sleep time; *REM*, rapid eye movement sleep; *SE*, sleep efficiency; *SpO₂*, oxygen saturation; *RDI*, respiratory disturbance index. Data are presented as mean (standard deviation; 95%CI).

Table 4: Respiratory parameters and EMG activity during sleep (EMGdi=NRD, primary outcome), expressed as percent of maximum activity at sea level, for inspiratory and expiratory muscles at sealevel and different altitudes (Night 1); only one sleep study was obtained at 5,570m. *ODI*, oxygen desaturation index; *SpO₂*, oxygen saturation. *EMG*, electromyography. Data are presented as mean (standard deviation; 95%CI).

Figure legends:

Figure 1: Periodic breathing while asleep in a healthy subject (BW) at 4,370m altitude. The inspiratory activity of the diaphragm EMG (EMGdi, mV) is clearly visible between the ECG artefacts in Channel 1, airflow indicates a central apnoea in Channel 2 (L/s). The decline in inspiratory EMGdi activity prior to the development of the apnoea can be described by the gradient of the 1st slope ($\Delta y1/\Delta x1$), the incline in inspiratory EMGdi activity following the apnoea is characterized by the gradient of the 2nd slope ($\Delta y2/\Delta x2$).

Figure 2: Transoesophageal electromyography of the diaphragm (Channel 1-5; EMGdi) and airflow during sleep at 4,370m of altitude. The EMGdi channel display ECG artefacts (QRS complex) as well as inspiratory EMG activity. Airflow is indicated by pressure changes (Channel 6). There is a clear crescendo-decrescendo pattern in the inspiratory EMGdi activity followed by absence of any inspiratory activity during central apnoea.